

HIGH SENSITIVITY TROPONIN - ITS USE IN DIAGNOSIS OF CARDIAC DYSFUNCTION



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ABSTRACT

Troponins are regulatory proteins and part of the contractile apparatus that is integral to muscle contraction in skeletal and cardiac muscle but not smooth muscle and are important clinically because cardiac troponins (cTn) are sensitive indicators of myocyte injury and have become integral to the definition of myocardial infarction. There are several issues surrounding the significance of troponin and how it should be used, both for the assessment of cardiac disease and in settings of non-cardiac illness. This thesis examines a number of these areas of uncertainty.

This thesis focuses initially on the analytical validation of troponin assays and I offer guidelines for a standardised approach to undertaking the verification of these analytical characteristics. I report on these characteristics for 2 highly sensitive assays and their application to a cardio-healthy population.

In the second part of this thesis I focus on the physiology of troponin in the normal population. I describe studies undertaken with a cohort of healthy children and demonstrate the significance of population coning when determining the 99th percentile of the upper reference limit using 2 highly sensitive troponin assays.

The final part of this thesis investigates the significance of troponin in the acute coronary syndrome (ACS) and non ACS setting. I offer a hypothesis suggesting that bleb formation is a mechanism for troponin release. I describe how improvements in sensitivity of troponin T assays allow better prognostic information regarding all cause mortality in end stage renal disease patients, demonstrate troponin release after strenuous exercise in elite cyclists and I describe a cross-sectional study looking at troponin concentrations in subjects with non cardiac illness and the general community. Using data mining techniques I demonstrate how

the use of a new high sensitivity troponin I assay can offer greater assistance to the clinician in stratifying patients at risk of a major adverse cardiac event (MACE). I provide evidence that suggests the use of a multi-marker approach to identifying patients at risk is potentially viable.

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DECLARATION

In this thesis I detail the findings from research carried out between July 2009 and August 2013. The research studies described in Chapters 3-5 were carried out in collaboration with my co-authors, the names of whom are listed at the start of each chapter. For each of these studies I took a lead role in the experimental design, subject recruitment, data collection and analysis, with all authors contributing to final submitted version of the manuscripts. I obtained assistance with these concepts from my supervisory panel members A/Professor Peter E Hickman, Professor Julia M Potter, A/Professor Brett Lidbury and Dr Alice Richardson.

I obtained assistance with and analysis with the mathematical approach to data mining from A/Professor Brett Lidbury and Dr Alice Richardson.

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DEDICATION

To my family, it was my mother's wish to see her two sons receive "*the floppy hat*".

Unfortunately she passed away before both my brother, Paul, and I completed our studies.

My dad will complete that wish for her.

To Anne, Liesel and Scott, thank you for putting up with the "Grumpy Gus" when he reared his head over the past few years and for the unconditional support.

shukran kabeer.

PUBLICATIONS AND PRESENTATIONS RELEVANT TO THIS THESIS

PEER REVIEWED JOURNAL ARTICLES

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SCIENTIFIC CONFERENCE AND MEETING PRESENTATIONS

- 2010 SW AIMS meeting, Canberra
“Troponin Past, Present and Future ?”
- 2010 AACB NSW/ACT Branch Meeting
“Evaluation of the Roche hs-TnT Assay”
- 2010 AACB SES, Sydney
“hs-TnT which reference intervals ?”
- 2010 AACB/AIMS Combined Annual Scientific Meeting, Perth
“Highly Sensitive TnT – An opening to a whole new world”
- 2011 Roche Cardiac Symposium, Heidelberg, Germany
“hs-Tn and Healthy Populations”
- 2011 Abbott New Zealand Architect User Symposium, Rotorua, NZ
“Highly Sensitive Troponin”
- 2012 Abbott Scientific Symposium. Sydney
“High Sensitivity troponin – its use in diagnosis of cardiac dysfunction”
- 2012 Abbott Scientific Symposium. Melbourne
“High Sensitivity troponin – its use in diagnosis of cardiac dysfunction”

AWARDS

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADAPT	Accelerated Diagnostic protocol to Assess Patients with chest pain
ADP	Accelerated diagnostic protocol
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
AMI	Acute myocardial infarction
APACE	Advantageous Predictors of Acute Coronary Syndromes Evaluation
ApEn	Approximate entropy
AUC	Area under curve
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CHD	Coronary heart disease
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiological Collaboration
CK-MB	Creatine Kinase MB isoenzyme
CLSI	Clinical Laboratory Standards International
CRP	C-reactive protein
cTn	Cardiac troponin
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CV	Coefficient of variation
CV _a	Analytical variation (imprecision)
CVD	Cardiovascular disease
CV _g	Between individual variation
CV _i	Within individual variation
CV _t	Total variation

ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimate of the glomerular filtration rate
EQA	External quality assessment
ESC	European Society of Cardiology
ESRD	End-stage renal disease
FDA	Food and Drug Administration
g	Gram
GET	Gas exchange threshold
GGT	Gamma glutamyl transpeptidase
HA	Heterophile antibody
HAMA	Heterophilic anti mouse antibody
HbA1C	Haemoglobin A1C
HRV	Heart rate variability
hs-cTnI	High sensitivity troponin I
hs-cTnT	High sensitivity troponin T
IFCC	International Federation of Clinical Chemistry
II	Index of individuality
IQC	Internal Quality control
ISO	International organisation of standards
kDa	Kilo Dalton
L	Litre
Ln	Natural log
LoB	Limit of blank
LoD	Limit of detection
LOOK	Lifestyle Of Our Kids
LoQ	Limit of quantitation
LVEF	Left ventricular ejection fraction
m	Metre
MACE	Major adverse cardiac event
MDRD	Modification of Diet in Renal Diseased
MDS	Classical multidimensional scaling
mg	Milligram

MI	Myocardial infarction
MW	Molecular weight
ng	Nanograms
NPV	Negative predictive value
NSTEMI	non ST-elevation myocardial infarction
NTproBNP	N-terminal pro B type natriuretic peptide
p	Probability
PCA	Principal components analysis
PoCT	Point of Care Testing
PPV	Positive predictive value
PSE	Prolonged strenuous exercise
QC	Quality control
RCV	Reference Change Value
RMSSD	Root mean squares of successive differences
ROC	Receiver operator curve
SD	Standard deviation
SE	Standard error
SEM	Standard error mean
STEMI	ST-segment-elevation myocardial infarction
SVM	Support Vector Machine
TIMI	Thrombolysis in Myocardial Infarction
Tn	Troponin
TnC	Troponin C
TnI	Troponin I
TnT	Troponin T
U	Units
ug	Micrograms
URL	Upper reference limit
VO ₂	Oxygen uptake